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The role of IL-33/ST2 system in the modulation of the immune response in infective endocarditis (a literature review)

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ABSTRACT

An inflammatory process accompanied by a considerable number of pathological conditions in the body is one of the symptoms of infective endocarditis. The components of the immune system involved in the inflammatory response may serve as markers determining the development and prognosis of the disease and as potential therapeutic targets. These components include cytokines IL-33, sST2, and the IL-33/ST2 system, which are actively involved in the modulation of the inflammatory response. At present, the role of these biologically active molecules is well described for various pathologies associated with tissue destruction, including cardiovascular diseases, but not for the pathogenesis of infective endocarditis. This review is aimed at analyzing the available information on the pathogenesis of infective endocarditis, the role of IL-33 and ST2 in the formation of the inflammatory response in various pathological processes, and changes in the expression of the genes encoding these proteins under the influence of various factors.

Key words: IL-33, ST2, interleukin, infective endocarditis, cardiovascular diseases, protein secretion, gene expression.

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Роль комплекса IL-33/ST2 в модуляции иммунного ответа при инфекционном эндокардите (обзор литературы)

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РЕЗЮМЕ

Процесс воспаления, который сопровождает немалое количество патологических состояний организма, является одним из формирующих комплекс симптомов инфекционного эндокардита факторов. Компоненты иммунной системы, участвующие в воспалительном ответе, могут являться маркерами, определяющими развитие и прогноз заболевания, а также могут быть потенциальными терапевтическими мишенями. К таким компонентам относятся цитокины IL-33, sST2 и рецепторный комплекс IL-33/ST2, принимающие активное участие в модулировании воспалительной реакции. На настоящий момент роль этих биологически активных молекул достаточно хорошо описана для различных патологий, связанных с деструкцией тканей, в том числе и при сердечно-сосудистых заболеваниях, но не для патогенеза инфекционного эндокардита.

Данный обзор направлен на анализ имеющейся информации о патогенезе инфекционного эндокардита, роли IL-33 и ST2 в формировании воспалительного ответа при различных патологических процессах и экспрессии генов, кодирующих эти белки под воздействием различных факторов.

Ключевые слова: IL-33, ST2, интерлейкин, инфекционный эндокардит, сердечно-сосудистые заболевания, секреция белка, экспрессия гена.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

The morbidity of infective endocarditis (IE) even in economically prosperous countries of Western Europe and the USA ranges from 25 to 93 per 1 million people, and the mortality rate from this disease remains high – from 18 to 36% according to various sources [1]. The incidence of IE in the Russian Federation is 3–10 cases per 100 thousand people per year [2]. Undoubtedly, IE is a heterogeneous disease characterized by a wide range of clinical manifestations, which depend on both an etiological agent and a complex of predisposing factors.

Based on the notion of IE as a systemic disease, the severity of which is largely determined by the immu-

nopathological processes associated with invasion and elimination of the pathogen, the primary task in determining the ways of its prevention lies in the search for key immunological factors that determine the body's resistance to pathogenic and opportunistic microorganisms. Components of the immune system, such as cytokines, immunoglobulins, components of the complement system, and others, are active participants in the inflammatory response induced by the introduction of a microbial agent. A key way to initiate an inflammatory response is to activate NF- κ B and MAPK signaling pathways, pathogen-associated molecular patterns (PAMPs) of microorganisms, and some cytokines (e.g., tumor necrosis factor- α (TNF α) and interleukin-1 (IL-1)).

We suggest that one of the risk modifiers for IE may be the ST2L transmembrane receptor (suppression of tumorigenicity 2 ligand). The ST2L protein is a member of the Toll/interleukin-1 superfamily – highly conserved intracellular signaling domains. Representatives of this family initiate innate immunity by activating the transcription factor NF-kappa B (NF-kB), which leads to the formation of pro-inflammatory cytokines. However, it was found that ST2L forms a heterodimeric complex for binding of IL-33 to IL-1R. The IL-33/ST2 signaling complex can stimulate the immune responses of both type 1 helper T cells (Th1) and type 2 helper T cells (Th2) depending on the type of the activated cell, microenvironment, and cytokine network in the damaged tissue [3]. At the same time, in experimental works, it was shown that IL-33, which is a member of the IL-1 family, could independently function as a modulator of the NF-kB signaling pathway activity and the Toll-like receptor (TLR)/IL-1R canonical signaling pathway [4, 5].

The aim of the research was to collect available information on the relationship between the IL-33/ST2 system and the polymorphism of genes encoding its components, the changes in their expression level and the pathogenesis of infective endocarditis.

SEARCH STRATEGY

This review includes data from relevant articles describing the role of gene polymorphism of the innate immune response and the features of their expression in patients with infective endocarditis, published from January 2008 to January 2018 and presented in the PubMed database. Search queries were formulated with the following word combinations: “infective endocarditis”, “gene expression”, “interleukin”, “cardiovascular diseases”, “protein secretion”. Search for publications not found with these combinations was performed using references in relevant articles.

INFECTIVE ENDOCARDITIS

Infective endocarditis (IE) is one of the multifactorial diseases. It comes second among the causes of the development of acquired heart defects. The key point in the formation of pathological changes in the valvular apparatus is an infection, usually of a bacterial etiology, which affects valvular and subvalvular heart structures and has an acute or subacute course [6, 7]. Microbial colonization is possible in damaged areas of native heart valves, or prosthetic structures. There is a probability of colonization of intracardiac implants and foreign intravascular prosthetic materials used

in a wide range of therapeutic surgical interventions for the correction of cardiovascular pathologies. The progress in conservative and surgical treatment, the emergence of new risk groups, and the formation of microorganism resistance to a wide range of antimicrobial agents have led to the emergence of new clinical manifestations of IE, which complicates timely diagnosis and worsens the prognosis of the disease. Infective endocarditis that is not associated with intravenous drug use is a disease that occurs in both men and women (however, the incidence of IE in men is three times higher) at any age (but the risks are higher for people over 50 years old) [8].

To date, more than 120 pathogens of infective endocarditis are known. The leading pathogens are gram-positive bacteria [2]. Most often, they are representatives of the *Streptococcus* (*Str. Viridans*, *Str. Bovis*, etc.), *Staphylococcus* (mainly *S. aureus*, *S. epidermidis*) and *Enterococcus* genera. In some cases, the pathogen may be fungi and bacteria from the HACEK group (*Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella*), other gram-negative bacilli, and sometimes cocci [9].

Normally, the endothelium of the valvular heart apparatus is resistant to bacterial colonization under conditions of periodic transient bacteremia [6]. For the development of IE not related to the intravenous administration of narcotic drugs, a number of independent factors are required. They include a change in the heart valve surface to obtain a suitable place for bacterial colonization; stable bacteremia, with a circulating pool of highly virulent microorganisms; creation of an infected mass by “burying” a proliferating microorganism in the protective matrix of fibrin and platelets, the presence of immunosuppressive states, including suppression of the immune response associated with stress (hypothermia, malnutrition and insufficient nutrition, chronic psycho-emotional stress); a genetic predisposition due to mutational variability of genes of different protein classes [8].

At the site of attachment of the bacterial colony, an inflammatory reaction can be expressed up to the level of abscess formation with the subsequent valve leaflet destruction. The formation of abscesses is a significant complication in IE, since abscesses can penetrate deeper into the fibrous rings and myocardium [10]. In addition to the deformation of the leaflet apparatus, spreading on the heart valve prosthesis leads to formation of fistulas, which can cause a complete separation of the prosthesis from the fibrous ring. The atrial surface of the mitral valve leaflets and the ven-

tricular surface of the aortic valve leaflets are places of an increased risk of vegetation attachment, as they are areas of high pressure.

The inflammatory response in the development of IE is systemic and stimulates the development of reactions of both an innate and adaptive immune response, starting with acute-phase proteins, complement system activation, increasing concentrations of circulating immunoglobulins of all classes, the appearance of macrophages in peripheral blood, and the synthesis of various types of circulating antibodies [11]. To control the growing infectious lesion, the host organism intensively produces opsonic antibodies, cryoglobulins, antibodies against bacterial heat shock proteins and macroglobulins, and complement-fixing and agglutinating antibodies. Antibodies against cell surface components reduce the adhesion of *C. albicans* to fibrin and platelets *in vitro* and reduce the incidence of IE *in vivo*. Recent data indicate the possible role of vaccination against the clumping factor A for the IE prevention in simulation studies [12]. However, an effective vaccine for humans has not been developed yet.

Thus, the pathogenesis of IE includes several factors: a pathogenic microorganism, damage to the surface of the native heart valve or the presence of a prosthetic heart valve, the activity of the immune response, and exogenous and endogenous factors, including individual susceptibility to infection [13].

Even though the clinical component of IE has been studied sufficiently, opinions on the etiology of this disease are split [13]. Besides, the trigger mechanism for the development of the pathological process is not well understood from the perspective of the immune response activation. Information on the immune response reactions, marker genes, and their expression during the inflammatory response in IE is changing [15]. At the same time, some researchers [15] demonstrate the correlation between gene polymorphism of the innate immune response and susceptibility to *S. aureus* invasion and an increased risk of native valve endocarditis development.

INTERLEUKIN-33 (IL-33)

Interleukin-33 (IL-33), a member of the family of pro-inflammatory cytokines (IL-1), enters the cytoplasm and extracellular space when the cell is damaged. IL-33 is secreted in endothelial cells, epithelial cells, and fibroblasts, both during homeostasis control and in inflammation. IL-33 acts as an alarm (alarmin activity) and is released upon cell destruction

or tissue damage to initiate immune cells [31]. IL-33 initiates and activates local inflammatory reactions by recruiting and activating cells that have functions associated with inflammation (eosinophils, basophils, and neutrophils), stimulates fibrogenesis and angiogenesis, affects vascular permeability (*in vitro* and *in vivo* models), and participates in the restoration of the mucous membrane integrity and wound healing [15].

The IL-33 gene is located on the 9p24.1 chromosome, with a length of 42,835 bases; it interacts with IL1RL1, USP21, GATA3, and other genes. The constant expression of IL-33 is registered in various types of epithelial cells, fibroblasts, smooth muscle cells, and mast cells [17]. The expression of IL-33 in macrophages is negligible, but its activation by anti-inflammatory factors, such as cell wall lipopolysaccharides, may appear [18]. A polymorphic variant of this gene with a mutation at rs7044343 is associated with the modulation of coronary heart disease [19].

Despite the fact that IL-33 belongs to the family of pro-inflammatory IL-1, the presence of immunoregulatory properties distinguishes it from IL-1 and the fibroblast growth factor, which obtained structural similarity to IL-33 [20]. Being an important member of the IL-1 family, IL-33 has pleiotropic effects in the formation of the innate and adaptive immune responses, and its level strictly correlates with the level of inflammation in the tissue [21]. At the same time, IL-33 can regulate the nuclear transcription of protein genes, which activate inflammation. IL-33 acts as a traditional cytokine by activation of NF- κ B via the ST2L/IL-1RAcP dimeric complex, or as an intracellular activator of a nuclear factor by translocation into the nucleus, where it binds to chromatin and modulates gene expression. IL-33 can act as an alarm when it is released after cell damage or as a negative regulator of NF- κ B gene transcription when it acts intracellularly [3]. IL-33 is synthesized in the form of a precursor with a molecular mass of 30 kDa. After propeptide cleavage influenced by the caspase 1 enzyme, it is transformed into a mature protein with a mass of 18 kDa. The precursor form is processed enzymatically and then initiates inflammation through the Toll-like receptor (TLRs) recognizing signaling system, acting as an alarmin [22]. However, synthesized IL-33 may not go through the maturation stage. In this case, it acts as a transcription inhibition factor due to the presence of a nuclear localization signal in the propeptide. The transcriptional repressor function, which is not characteristic of the cytokine family, is realized through bonds with the surface of the nucleosome in the pocket

region formed by histones H2A and H2B [20]. Also, IL-33 can serve as a non-histone chromosomal protein involved in the assembly of nucleoprotein complexes, supporting and strengthening the chromatin structure, which affects the gene expression rate in these chromosome regions. IL-33 is expressed by both immune cells, for example, macrophages and dendritic cells, and non-immune ones – endothelial and epithelial cells, and fibroblasts [21]. Unlike other members of the IL-1 family, IL-33 primarily induces Th2 immune responses and macrophage polarization through an alternative activation pathway (the so-called M2 macrophages) [10]. The release into the extracellular space occurs after tissue damage [23] and is accompanied by Th2 initiation and stimulation of the secretion of associated cytokines (IL-4, IL-5, and IL-13), as well as by activation of the innate immune response cells – mast cells and lymphoid cells of the innate immune response (innate lymphoid cells, ILCs).

To activate the NF- κ B and MAPK via the MyD88-dependent signaling pathway, IL-33 binding to the plasma membrane receptor [3], consisting of ST2L receptor proteins (tumor suppressor ligand 2) and IL-1RAcP (interleukin 1 receptor auxiliary protein), is required. In addition to its role in the autoimmune response, which is the most studied [24], IL-33 is involved in the inflammatory processes accompanying various cancer, pulmonary, intestinal, and cardiovascular diseases [25]. There is also evidence of its role in the pathogenesis of Alzheimer's disease [26]. However, despite the obvious immunoregulatory effect on the course of IE, the participation of IL33 in the pathogenesis of this inflammatory disease is not described.

SUPPRESSION OF TUMORIGENICITY 2 (ST2)

The suppression of tumorigenicity receptor (ST2), also known as IL1RL1, T1, DER4, or Fit-1, is a member of the interleukin family. The IL1RL1 gene is located on the long arm of the 2q12 chromosome and contains 11 exons. IL1RL1 can perform the functions of an immunomodulator, therefore it is expressed both as a receptor attached to a membrane, activated by IL-33, and as a soluble variant (sST2), which exhibits anti-inflammatory properties.

As a result of alternative splicing of IL1RL1, ST2 can be expressed in four functional isoforms: ST2L (membrane-bound form), sST2 (soluble form), ST2V – an isoform similar to sST2 but lacking the third extracellular domain of immunoglobulin [27], and ST2VL with a transmembrane domain. ST2L is expressed by

various immune cells, such as mast cells, monocytes, dendritic cells, and is selectively expressed on Th2 cells, but not on Th1 lymphocytes [28].

In addition to the expression of ST2L on the surface of many immune cells (lymphocytes (Th2), natural killer (NK) cells), the expression of this receptor on the surface of myeloid cells, such as monocytes, dendritic cells and granulocytes, was identified [3]. It was found that the effects of ST2L are realized through the negative control of IL-1RI and TLR4, which consists in blocking the MyD88 and Mal adaptor proteins. This blocking leads to the inhibition of TLR signaling and promotes the development of a Th2 immune response. However, the control does not extend to the TLR3 signaling pathways and does not affect the transcription factor of type III interferons (IFNs), which makes it possible to further regulate the inflammatory response to virus infection through activation of interferon alpha and beta (IFN α , - β) transcription, as well as through other interferon-induced genes.

At the same time, sST2 binding to IL-33 leads to blocking of the signaling pathway along the IL-33/ST2L axis [30] and reduces anti-inflammatory effects, thus eliminating the cardioprotective effect. It is believed that the soluble form of ST2, as an IL-33 trap, plays a crucial role in several autoimmune diseases, including systemic lupus erythematosus, sclerosis, and rheumatoid arthritis [30, 32]. Being a mechanically induced cardiomyocyte protein, sST2, depending on its level in the serum, can predict the outcome in patients with acute myocardial infarction or chronic heart failure. The sST2 can also disrupt cardiac function and exacerbate heart remodeling in both non-ischemic and ischemic tissues. In addition to the role of IL-33/ST2L as a therapeutic target, sST2 has also been identified as a biomarker of ischemic heart disease in humans [33]. It was shown that the introduction of the sST2-Fc fusion protein can be useful in the treatment of arthritis, pulmonary eosinophilia, shock, liver, and intestinal ischemic reperfusion injury [34, 35]. It was found that sST2 blocks the production of pro-inflammatory cytokines, such as IL-6, IL-12, and tumor necrosis factor-alpha (TNF α) by macrophages, caused by lipopolysaccharides (LPS) of the cell walls of gram-negative bacteria, but does not affect the production of IL-10. It was also revealed that genetic variants that change the intracellular transmembrane signaling of ST2 can express human sST2, opening a new pathway of immune and inflammatory regulation [36].

Thus, it has been proven that ST2 can regulate the inflammatory response to tissue damage mainly by modulating signaling of the MyD88 and Mal adaptor receptors, which is directly related to the nuclear factor NF- κ B from the TLR activation pathway. TLRs are the main receptors of the innate immune response that recognize elements of the bacterial cell walls and associated mechanisms of inflammation activation in response to bacterial invasion, including the formation of conditions for valve structure colonization by the opportunistic *Streptococcus bovis*/*Streptococcus equinus* complex associated with the immune evasion [37]. Due to this fact, the participation of the ST2 protein in the pathogenesis of IE seems logical. However, this direction has not acquired sufficient attention.

RECEPTOR COMPLEX IL-33/ST2

As mentioned earlier, one of the factors of the NF- κ B pathway activation which is accompanied by stimulation of Th1 or Th2 immune responses, depending on the type of the activated cell, microenvironment, and cytokine content in the damaged tissue, includes the IL-33/ST2L complex [3]. In experimental models of one study, it was found that the development of type 1 diabetes, experimental autoimmune encephalomyelitis, fulminant hepatitis, and breast cancer was accompanied mainly by the Th1/Th17 immune response. At the same time, a higher level of IL-33 production was recorded [3]. M. Milovanovic et al. suggested that IL-33, in a manner independent of its receptors, may contribute to the development of inflammatory autoreactive immune responses.

It is noteworthy that the receptor for IL-33 is a heterodimeric complex consisting of the membrane-bound ST2L protein and the IL-1RAcP co-receptor. The basis of the effector initiation of Th2-type responses is the activation of the ST2L receptor, which, despite its membership in the TIR family, is not involved in the activation of NF- κ B. The initiation of inflammatory reactions through the IL-33/ST2 receptor complex occurs due to the signal-conducting co-receptor IL-1RAcP and depends on the type of cell and microenvironment. Various signaling pathways activated by IL-33, including MyD88, IL-1R-associated kinase 4 (IRAK4), and TRAF6, have been described [38]. With the use of the downward pathway through CT2, MyD88, and TRAF6 adapters, activation of NF- κ B and mitogen-activated protein kinases, which are involved in the control of cell proliferation and apoptosis, is ultimately possible [38]. Members of the mTOR pathway, such as phosphoinositide-3-ki-

nase (PI3K), can also be activated by IL-33 in Th2 cells, macrophages, or eosinophils [39], which positively correlates with the expression of IL-33 and sST2 genes in myocardial infarction [40].

The IL33/ST2L signaling pathway is also regulated by other mechanisms, for example, IL-1RAcP alternative splicing, and affects the severity of the inflammatory response, since signaling depends on the functional state of both components [41]. IL-1RAcP is also important for IL-1-induced activation of interleukin-1 receptor-associated kinase (IRAK) and stress-activated protein kinase (SAPK). The recombinant chimeric sIL-1RAcP-Fc protein has been found to decrease IL-6 secretion in mast cells exposed to IL-33 [41]. K. Hong et al. showed that co-incubation of sST2-Fc and sIL-1RAcP-Fc synergistically inhibited the activity of IL-33, indicating the role of sIL-1RAcP in modulating the biological activity of IL-33.

At the same time, the ST2 ligand-binding chain with the component for interacting with IL-33 and the soluble ST2 have antagonistic properties. This mechanism allows to regulate the inflammatory response activation in various types of cells and tissues. However, it is assumed that an additional, different from IL-1RAcP and ST2, receptor component that can participate in the regulation of the biological activity of IL-33 exists [41]. It is suggested that such a component involved in the activation of the signaling pathway is an Ig IL-1R-related molecule (SIGIRR) interacting with IL-1RR (SIGIRR), a member of the IL-1R family, which is involved in the regulation of IL-18, IL-1, and IL-33 signaling. In Th-2 cells exposed to IL-33, dimerization of SIGIRR with ST2L negatively regulates IL-33/ST2 signaling through direct interaction with the intermediate signaling block of the IL-1R family. The IL-1R and IL1RAcP complex blocks downward signaling through the extracellular domain of IL-33 or by its interaction with MyD88, IRAK, and TRAF6 [42].

THE ROLE OF THE IL-33/ST2 COMPLEX IN THE INFLAMMATORY RESPONSE

As described above, the IL-33/ST2 complex can have both pro-inflammatory and anti-inflammatory effects. Elevated levels of soluble ST2 may indicate a risk of developing graft-versus-host disease (GVHD) and its further mortality. Elevated levels of IL-33 in mice after conditioning and in patients during GVHD were shown in a study by D.K. Reichenbach et al. [43]. IL-33/ST2 activation was performed on murine and human alloreactive T cells. It was shown that

sST2 concentration increased as experimental GVHD progressed. Blocking IL-33/ST2 interactions during transplantation of allogeneic hematopoietic cells by exogenous ST2-Fc infusions was characterized by a decrease in mortality during GVHD. This fact indicates that ST2 acts as a trap receptor that modulates GVHD.

Studies have also shown the important role of IL-33 and ST2 in the inflammatory processes of the respiratory system. For example, IL-33 level correlates with the severity of clinical asthma [43], since IL-33 increases the level of type 2 cytokines that mobilize eosinophils and polarize M2 macrophages. Probably, the same mechanism is present in an increase in the IL-33 concentration in patients with atopic dermatitis who have quite high IL-33 level in the skin epidermis [44].

Endometriosis is a chronic condition that is classified by the abnormal growth of endometrial tissue outside the uterus. Although the pathogenesis of this disease remains unknown, it is noted that patients with endometriosis have immune dysfunction. J.E. Miller et al. [45] investigated the role of IL-33 as a regulator of chronic inflammation, which plays a critical role in the pathology of endometriosis, using patient tissue samples, cell lines, and a syngeneic mouse model. It was found that in the tissue with endometriosis, significantly higher levels of IL-33 protein are observed compared to the endometrium of healthy fertile organs. In vitro stimulation of IL-33 led to the production of pro-inflammatory and angiogenic cytokines. In the syngeneic mouse model of endometriosis, injections of IL-33 caused systemic inflammation, resulting in an increase in pro-inflammatory plasma cytokines compared to the control group. In addition, endometriotic lesions in IL-33 treated mice were highly vascularized, while the cells involved in this process showed increased proliferation. The authors provided strong evidence that IL-33 stimulates inflammation, angiogenesis, and proliferation in the endometrium.

Cigarette smoke causes lung epithelial cells to produce intracellular IL-33 more intensively, which is released after cell damage by a viral or bacterial infection. At the same time, the production of ST2 by congenital type 2 cells is reduced, but its expression by macrophages and NK cells is increased, which leads to a halt in the production of type 2 cytokines by ILC2 and inhibition of IL-12 production by macrophages [46].

It has been shown that the expression of IL-33 and ST2 increases in the gingival tissue in patients with chronic periodontitis and COPD, which makes them

potential therapeutic targets. In contrast, IL-33 plays an important role in uveitis, which is an auto-inflammatory disease affecting the eyes. Treatment with IL-33 medications reduced the severity of experimental autoimmune uveitis in mice, thus, suggesting the possibility of using recombinant IL-33 to treat autoimmune uveitis and autoimmune diseases in general [47].

In recent years, knowledge about the role of IL-33, sST2, and the IL-33/ST2 complex in the pathophysiology of cardiovascular diseases has expanded. Data on the association of these proteins with dysfunction, fibrosis, and myocardial remodeling have appeared. In this regard, the beneficial effects of IL-33 are realized through the ST2L receptor. When IL-33 binds to sST2, the interaction between ST2L is interrupted and antiremodeling effects are eliminated [48].

Besides its role in myocardial remodeling, the IL-33/ST2 system, presumably, plays an additional role in the development and progression of atherosclerosis. It is suggested that the IL-33/ST2L complex may have therapeutic potential for the beneficial regulation of myocardial response to overload and trauma [47]. It was shown that after MI, sST2 expression increases rapidly during the first 4 weeks and, unlike IL-33, its levels correlate with the processes of fibrosis and inflammation. The obtained data indicate the differential regulation of IL33 and sST2. The therapeutic modulation of early sST2 expression may be more important to prevent unfavorable remodeling after MI [49].

One part of the Framingham study showed that elevated serum sST2 levels are associated with genetic determinants and correlate with an increased risk of cardiovascular diseases [50]. With the participation of 2,991 individuals, the authors were able to establish that differences in sST2 levels are caused to a greater extent by genetic factors than by clinical and environmental ones. The GWAS (genome-wide association study) demonstrated multiple associations between single nucleotide polymorphism (SNP) in different parts of the IL1RL1 gene and sST2 concentrations. Five missense mutation variants of IL1RL1 showed a correlation with higher levels of sST2 and were found in exons encoding the intracellular domain of ST2, which is absent in sST2. The authors show that the genetic variation of IL1RL1 can lead to an increase in sST2 levels and alter immune and inflammatory signaling via the ST2/IL-33 pathway.

In a study involving individuals in the Chinese Han population, a relationship between polymorphisms of the IL-33/ST2 signaling pathway and MI was found [51]. An analysis of the case-control study with the par-

participation of 490 patients with MI and 929 individuals in the control group was carried out. The relationship between the polymorphic variants of IL33, IL1RL1, and IL1RaP (rs11792633, rs1041973, rs4624606) and the risks of developing MI was studied. Based on an associative study, it was concluded that in the IL33/ST2 signaling pathway, the minor allele of polymorphism rs4624606 IL-1RaP is a potential independent risk factor for MI.

The role of IL33 as an alarmin in activating the dependent Th2-type response in the development of obesity, viral infections, immunological deficiency, intestinal inflammation, suppression of tumor growth [52], and cytomegalovirus infection has been demonstrated [53].

Thus, many authors have shown that the IL33/ST2 immune receptor complex is one of the first to be included in pathological changes, both in diseases associated with tissue damage and in response to microbial invasions. The functioning of the complex consists not only in the activation of the innate immune response along the effector pathway but also in the development of an inflammatory response along the Th2 activation pathway. The latter is accompanied by a decrease in the local inflammatory response, which may be associated with an increased risk of microbial adhesion on the valvular heart apparatus and the development of infective endocarditis.

Since IL-33/ST2 activation effects are multidirectional and depend on many external factors, including tissue and microenvironment, its role in modulating the inflammatory response is undeniable. Currently, insufficient attention is paid to the role of the IL-33/ST2 signaling complex in infectious pathologies of bacterial nature.

EXPRESSION OF MRNA AND IL-33/ST2 PROTEINS IN CARDIOVASCULAR DISEASES

Even at early stages of studying the immune response through the IL33/ST2 system [54], using the real-time polymerase chain reaction (real-time PCR) method, it was found that the IL1RL1 gene is actively expressed in hematopoietic cell lines. It was also actively expressed in the helper lines of T cells in the lymphocyte culture lines. It was found that mouse cell lines with Th1 lymphocytes do not express ST2 mRNA. On the other hand, one of the Th2 cell lines, D10, expressed ST2L (transmembrane form) without stimulation, while co-stimulation of PMA and A23187 induced ST2 (soluble form) of mRNA. These results indicate that the ST2 gene is involved in the regulation

of the immune system. IL-1 α , IL-1 β , and the receptor antagonist did not bind to the ST2L protein, which prompted the authors to search for a specific ST2 ligand. In the experiment, the recombinant human ST2 protein was purified and labeled with FITC. As a result, labeled human ST2 bound to RPMI8226 cells derived from myeloma was detected among various B cell lines, indicating the possible involvement of ST2 in T cell/B cell interaction.

Inflammatory cytokines, including IL-33/ST2, are involved in the regulation of adaptive and non-adaptive changes in the heart. Since cardiac fibrosis is largely dependent on increased production of extracellular matrix by cardiac fibroblasts, J. Zhu et al. [55] suggested that IL-33 inhibits the pro-fibrous activity of these cells directly. However, the concentration of IL-33 did not affect the expression of genes encoding the components of the extracellular matrix, or proliferation (typical of fibrosis markers). In a simulation study in mice, it was demonstrated that IL-33 is predominantly produced by myocardial fibroblasts, rather than by cardiac myocytes. This study showed that when knocking out the ST2 gene, mice are more susceptible to TAC-induced cardiac hypertrophy. Another study by D. Shao [56] showed that knocking out IL-33 disrupts the active system that protects the myocardium from cardiac remodeling events, such as cardiomyocyte hypertrophy and cardiac fibrosis induced by mechanical stress.

Modulation of the IL-33/ST2 system in post-infarction heart failure in rats showed increased levels of mRNA expression during myocardial infarction for IL-33 and sST2, but their different kinetics [49]. IL-33 mRNA expression was high immediately after acute myocardial infarction (AMI) and remained elevated for the first 12 weeks after AMI, which was accompanied by an increase in IL-33 protein expression. In contrast, sST2 mRNA expression showed an early peak 1 week after AMI, followed by a dramatic decrease in the first 4 weeks. Although sST2 expression showed an early peak and a positive correlation with markers of fibrosis and inflammation, IL-33 expression levels remained high over the entire observation time and did not correlate with these markers [48]. Cultivating human primary cardiac fibroblasts and human primary cardiac myocytes, P.T. Veeraveedu et al. [57] measured the mRNA, IL-33, and ST2 protein expression levels in cells and examined the effect of cytokines on the expression of these genes. Pro-inflammatory cytokines increase the expression of IL-33 in cardiac fibroblasts of the heart, cardiac myocytes, and vascular

smooth muscle cells through the pathways of NF- κ B and MEK, which proves its participation in inflammatory processes of the cardiovascular system. Besides, it has been shown that IL-33 is released during necrosis of human cardiac and smooth muscle cells.

In *in vivo* experiments, knockdown of IL-33 in normal endothelial cells of the human pulmonary artery led to the induction and expression of sST2. This is associated with the action of IL-33 as a nuclear suppressor for reducing sST2 expression by binding to homeobox regions and potentially recruiting transcriptional repressor proteins. As a result, a study by D. Shao et al. [56] showed that a significant loss of IL-33 occurs without its release from the cells in idiopathic pulmonary arterial hypertension.

Therefore, IL-33 enhances immune responses and inflammation, depending on the reactions of the immune response cells. On the other hand, the effects of IL-33 are associated with the induction of the Th2-type immune response through its ST-2 receptor. IL-33 is also a nuclear repressor factor. ST2, in turn, is expressed both as a variant of the ST2-membrane-dependent receptor activated by IL-33 and as a soluble sST2 variant, which manifests itself as a receptor trap and has anti-inflammatory properties. Despite the studied participation of the IL33/ST2 complex in many pathological processes, including asthma, rheumatoid arthritis, inflammatory bowel diseases, and more recently, cancer, Alzheimer's disease, cognitive disorders, and malaria [58], the involvement of this complex in the inflammatory response in infectious diseases is not clear.

CONCLUSION

The accumulated data on the participation of IL-33, sST2, and the IL-33/ST2 receptor complex in inflammatory and cardiovascular diseases prove the significant role of these cytokines in the inflammatory response in tissue damage and viral infection. However, the question of their participation in the pathogenesis of infective endocarditis is neglected. Like all cytokines, IL-33 and ST2 function more actively at low concentrations, and, therefore, their functionality remains unknown when their concentration changes during IE, which is inevitably accompanied by a change in local cytokine status and destruction of valve tissue. The problem of a quantitative assessment of gene expression and protein secretion of these interleukins in case of heart valve infection remains relevant.

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